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An unusual cause of "pink diaper" in an infant: Answers

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Urinary crystals; Pinkstained; diapers; Hypouricemia; Fractional excretion of uric acid; Hereditary xanthinuria

Answers

1. The possible etiologies of crystalluria in an infant include hypercalciuria, distal RTA (d-RTA), primary hyperoxaluria, cystinuria, hyperuricosuria and rarely due to increased excretion of other purine and pyrimidine metabolites such as 2,8-dihydroxyadenine, xanthine, hypoxanthine and orotic acid[1]. Our patient did not have evidence of metabolic acidosis, hypercalciuria, hypocitraturia, hyperoxaluria or aminoaciduria thereby ruling out crystalluria secondary to disorders causing hypercalciuria, d-RTA, primary hyperoxaluria, and cystinuria. We therefore focused further investigation on disorders of purine metabolism which can present with altered uric acid levels in plasma and urine [2]. Hyperuricosuria may be physiologic due to increased excretion of uric acid in neonates. Hyperuricosuria with hyperuricemia may be associated with hypoxanthine-guanine phosphoribosyl transferase (HPGRT) deficiency and glycogen storage disorders. Hypouricosuria can be seen in xanthine dehydrogenase (XDH) deficiency which is associated with increased excretion of xanthine and hypoxanthine. Adenine phosphoribosyl transferase (APRT) deficiency leads to increased urinary 2,8-dihydroxyadenine (2,8-DH) with uric acid excretion being normal [3].

2. Further testing should include:

- Urinary uric acid-to-creatinine ratio and fractional excretion of uric acid (FeUA).
- APRT enzyme activity in erythrocyte lysates – abolished enzyme activity confirms APRT deficiency.
- Urinary xanthine- and hypoxanthine-to-creatinine ratios – increased excretion and low FeUA is suggestive of xanthinuria

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- Urine sulfocysteine (SO) level to evaluate for molybdenum cofactor deficiency, which can be associated with xanthinuria.

In our patient, increased urinary excretion of xanthine and hypoxanthine and low FeUA along with severe hypouricemia, normal APRT enzyme activity and normal SO level, were diagnostic of hereditary xanthinuria.

3. Hypouricemia can be associated with several conditions which can be further classified based on FeUA. Low FeUA is seen in hereditary xanthinuria and is also associated with the use of allopurinol or rasburicase, and low dietary purine intake. Hypouricemia with normal to high FeUA is seen in hereditary renal hypouricemia, syndrome of inappropriate antidiuretic hormone, and conditions causing generalized proximal tubulopathy such as Wilson's disease, Fanconi syndrome and cystinosis [4]. Hypouricemia to the degree of severity seen in our patient is rarely seen in conditions other than xanthinuria or hereditary renal hypouricemia while patients with APRT deficiency have mild hypouricemia.

Commentary

Urinary crystals in this patient did not resemble uric acid or cystine crystals and in fact, did not resemble any commonly found urinary crystals. Literature review revealed the crystals to closely resemble 2,8-DHA almost exclusively seen in patients with untreated APRT deficiency. APRT deficiency (OMIM: 614723) is a rare, inherited disorder of purine metabolism that leads to excessive urinary excretion of the highly insoluble 2,8-DHA crystals which causes kidney stones, chronic kidney disease and even end-stage renal disease. Diagnosis is confirmed by stone infrared spectrophotometry and measurement of APRT activity in red blood cell lysates which can be abolished or diminished[5, 6]. Serum uric acid level is normal or mildly reduced in patients with normal kidney function and FeUA is normal [3, 6] [Unpublished observation, V. Edvardsson Jan 20, 2015]. Although the proband's crystals resembled 2,8-DHA, his APRT enzyme activity in erythrocyte lysate was normal at 36 nmol/h/mgHB (reference range 17–32 nmol/h/mgHB) excluding this diagnosis.

The findings of increased urinary excretion of xanthine and hypoxanthine, at 203 mmol/mol creatinine (Cr) (reference <53mmol/mol Cr) and 414 mmol/mol Cr (reference <49mmol/mol Cr), respectively, extremely low fractional excretion of uric acid at 0.25% (normal 7.28±2.9%) and the severe hypouricemia in our patient were highly suggestive of hereditary xanthinuria. Urine sulfocysteine level was normal at 7 micromol/g Cr (reference range <80micromol/g Cr) thus ruling out molybdenum cofactor deficiency as the cause of xanthinuria. Genetic testing of the proband revealed one previously described heterozygous mutation, T910M, in exon 25 of the xanthine dehydrogenase *(XDH)* gene (c.2729C>T) and a second, previously unidentified, heterozygous variant, R830C, in exon 23 of the *XDH* gene (c.2488C>T). [7, 8]. The proband's asymptomatic mother was heterozygous for the T910M mutation and his asymptomatic father was heterozygous for the R830C variant.

Further management of our patient involved a low purine diet in addition to maintenance of hydration especially in the face of an acute illness. One and a half year after initial presentation, body weight has increased to the 27th percentile and height to the 61st

percentile. The child is mostly asymptomatic but is still noted to have crystals in first morning urine samples, especially during episodes of acute illness. Microscopic examination of first morning urine specimens on multiple occasions has failed to show any crystals during illness free periods. However, urine xanthine- and hypoxanthine-to-creatinine ratios (mmol/mol) remain elevated at 731 and 248, respectively. Repeat renal ultrasound examinations have been normal.

Hereditary xanthinuria is an autosomal recessive disorder of purine metabolism most commonly manifesting with urolithiasis and in rare cases, renal failure due to crystal nephropathy [9]. The disorder is caused by mutations in the *XDH* gene located on chromosome 2p23 causing deficiency of the XDH enzyme responsible for degradation of hypoxanthine and xanthine to uric acid [10]. Deficiency of XDH results in markedly diminished production of uric acid and elevated xanthine and hypoxanthine levels in plasma and urine (Figure 1). High renal clearance and extreme insolubility at any physiological pH can cause xanthine crystal precipitation in the renal tubules leading to crystalluria, hematuria, urorolithiasis, and in severe cases, renal failure [9]. Infants can additionally present with urinary tract infection and failure to thrive. No satisfactory explanation for the latter association is available in the literature. Renal manifestations can present at any age, with more than 50 percent occurring in children younger than 10 years of age. In older patients, accumulation of xanthine in extra-renal tissues may cause duodenal ulcers, myopathy or arthropathy. About 20 percent of patients have been reported to be asymptomatic [9]. The incidence appears to be higher in Mediterranean and Middle Eastern populations [11, 12].

Hereditary xanthinuria is classified into two types based on the type of enzyme deficiency. In type I (OMIM 278300), there is an isolated deficiency of XDH whereas in type II (OMIM: 603592), there is an additional deficiency of the enzyme aldehyde oxidase (AOX) responsible for metabolism of allopurinol [13]. Diagnosis is made by identification of crystals, high urinary xanthine and hypoxanthine levels, low serum uric acid levels and low FeUA. Genetic testing is also available. To date there are seven reported mutations causing xanthinuria type 1 in the Human Gene Mutation Database (HGMD®) [14]. Four of these are nonsense or missense mutations, two are small deletions and one constitutes a small insertion [7, 10, 12, 15–17].

Xanthinuria can also be associated with molybdenum cofactor deficiency (OMIM: 252150) where sulfite oxidase (SO) is also inactive in addition to XDH and AOX and is characterized by severe neurologic involvement. Molybdenum cofactor is essential for the function of the SO, XDH and AOX. Diagnosis is made on the basis of hypouricemia and elevated urinary xanthine and S-sulfocysteine levels [18].

Hereditary xanthinuria is managed with high fluid intake and a diet low in purines. Urine alkalinization is ineffective as xanthine is insoluble at any physiological pH. Response to treatment can be monitored by urine microscopy looking for crystalluria, and by periodic monitoring of urinary xanthine and hypoxanthine excretion.

Conclusion

This clinical quiz highlights the importance of urine microscopy performed by the clinician for detection of crystalluria. It is important to examine a first morning specimen for the best yield. It is alarming to note that manual urine microscopy is not routinely performed in many nephrology practices and comes at the cost of losing valuable information gained from this simple procedure [19]. Importantly, this case also underscores the significance of severe hypouricemia as an important laboratory finding that can aid in diagnosis of a child presenting with urinary crystals.

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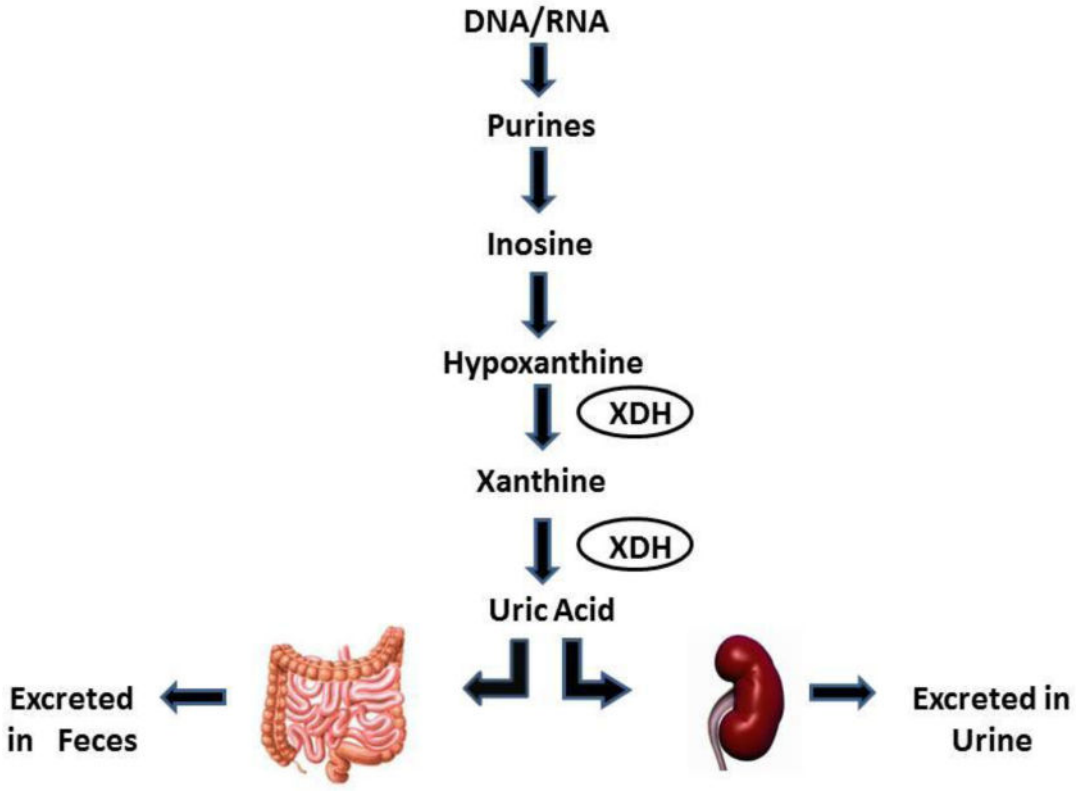

Figure 1.

Schematic overview of purine metabolism.

Abbreviations: DNA, deoxyribonucleic acid; RNA, ribonucleic acid; XDH, xanthine dehydrogenase.